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RESPONSE w/E.O.T. 3 mos.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:	Young, et al.
Serial No.:	09/237,291
Filed:	January 25, 1999
For:	Expanded and Genetically Modified Population of Hematopoietic Stem Cells
Group:	1635
Examiner:	Schmidt

Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

In response to the Final Rejection dated August 13, 2001, reconsideration of the above-identified application is respectfully requested.

The claims stand rejected under 35 U.S.C. 103 as being unpatentable over Murray, et al., Nakahata, Hoffman, et al., Fei, et al., or Davis, et al., in view of Ku, et al., Kobayashi, et al., Ramsfjell, et al., Ohmizono, et al., Szilvassy, et al., Escary, et al., or Bodine, et al., and further in view of Tushinski, et al., Fletcher, et al., Bello-Fernandez, et al., Hatzfeld, et al., and Hanenberg, et al. or Henenberg, et al. This rejection is respectfully traversed.

The present invention is directed to methods for genetically modifying human hematopoietic stem cells by contacting a vector comprising a polynucleotide sequence encoding a heterologous gene with a population of hematopoietic stem cells cultured with fibronectin and in the presence of an effective amount of an mpl ligand, an flt3 ligand (as

defined in Claim 18), or an effective amount of a thrombopoietin ligand, an f/t3 ligand, and Interleukin-6 (as defined in Claims 23 and 37). The vector may be a retroviral vector, an adenoviral vector, or an adeno-associated viral vector.

The Examiner has engaged in impermissible, hindsight reconstruction to pick and choose among the prior art in order to try to fashion a rejection of the claimed invention. (See Interconnect Planning Corp. v. Feil, 227 U.S.P.Q. 543 (C.A.F.C. 1985), at 551; Uniroyal Inc. v. Rudkin Wiley Corp., 5 U.S.P.Q.2d 1434 (C.A.F.C. 1988); In Re Dow Chemical, 5 U.S.P.Q.2d 1529 (C.A.F.C. 1988), at 1532; In Re Fine, 5 U.S.P.Q.2d 1596 (C.A.F.C. 1988), at 1600.)

The Examiner asserts that a person of ordinary skill in the art would have been motivated to culture human HSCs by the methods taught in the relevant cited patents and articles, to transfect them with genes using retroviral vectors as taught by the relevant cited articles, and to increase transduction efficiency through the use of fibronectin, also as taught by the relevant cited articles; however, the Examiner is required to show how and why the Applicants would have been motivated to combine the references in the manner combined by the Examiner. The Examiner has not done so. She has simply made unsupported statements regarding the asserted motivation of a person of ordinary skill in the art to undertake the components of the claimed invention.

On page 6 of the Office Action, the Examiner asserts that a person of ordinary skill in the art: (1) would have had an expectation of success to culture HSCs in the various factors specified in the claims; (2) would have had an expectation of success to modify such HSCs in culture using retrovirally-mediated gene transfer; and (3) would have had an expectation of success to increase transformation efficiency of the retroviruses through the use of

fibronectin; however, the question with respect to patentability of the claimed invention is **not** whether a person of ordinary skill in the art would have had a reasonable expectation of success with respect to individual components of the claimed invention, but whether that person would have had a reasonable expectation of success with regard to the combination of all of the components of the invention, i.e. whether the **invention as a whole** were obvious. The Examiner has not shown that the **invention as a whole** was obvious. In fact, the Applicants remind the Examiner of her statements of record in her Office Action of May 12, 1999, where, at the bottom of page 5, she stated that "There is a high level of unpredictability in the transgenic stem cell art for expression of transgenes in cultured stem cells." Given this unpredictability, a person of ordinary skill in the art would not have had a reasonable expectation of success with respect to the claimed **invention as a whole**. (In Re Wright, 6 U.S.P.Q.2d 1959 (C.A.F.C. 1988), at 1962.)

Furthermore, the Examiner has not shown how the cited references teach the concentration ranges recited in the claims. The Examiner has cited references where certain factors in the claims were used at certain concentrations, but she has made no showing of how the references teach the recited **ranges** of concentrations.

Finally, the Applicants note that claims 35, 44, and 51 are directed to $CD34^+$ $Thy\text{-}1^+$ Lin^- HSCs. The Examiner has not shown how the cited references teach the genetic modification of these particular HSCs in the presence of the factors and at the concentration ranges recited in the claims.

For the above reasons and others, this application is in condition for allowance, and it is therefore respectfully requested that the rejection under 35 U.S.C. 103 be reconsidered and withdrawn and a favorable action is hereby solicited.

Respectfully submitted,

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